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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference P37825WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/GB2004/004336	International filing date (day/month/year) 13.10.2004	Priority date (day/month/year) 14.10.2003	
International Patent Classification (IPC) or both national classification and IPC C07D209/30, A61K31/404, A61P43/00, C07D403/12, C07D401/12, C07D417/12			
Applicant OXAGEN LIMITED			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 7 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 09.05.2005		Date of completion of this report 29.07.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized Officer Diederen, J Telephone No. +31 70 340-1097 	

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IP20 Rec'd PCT/TO 28 MAR 2006

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB2004/004336

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, Pages

1-37 as originally filed

Claims, Numbers

1-30 received on 09.05.2005 with letter of 09.05.2005

Drawings, Figures

1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB2004/004336**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-30
	No: Claims	
Inventive step (IS)	Yes: Claims	1-30
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-30
	No: Claims	

2. Citations and explanations

see separate sheet

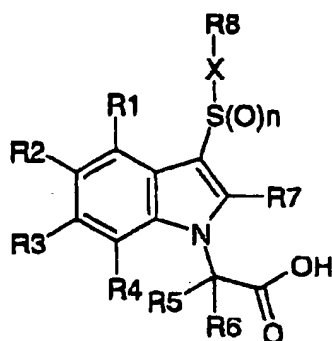
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CLAIMS

I. A compound of general formula (I)



I

wherein

R¹, R², R³ and R⁴ are independently hydrogen, halo, C₁-C₆ alkyl, -O(C₁-C₆ alkyl), -CON(R⁹)₂, -SOR⁹, -SO₂R⁹, -SO₂N(R⁹)₂, -N(R⁹)₂, -NR⁹COR⁹, -CO₂R⁹, -COR⁹, SR⁹, OH, -NO₂ or -CN;

each R⁹ is independently hydrogen or C₁-C₆ alkyl;

R⁵ and R⁶ are each independently hydrogen, or C₁-C₆ alkyl or together with the carbon atom to which they are attached form a C₃-C₇ cycloalkyl group;

R⁷ is hydrogen or C₁-C₆ alkyl

n is 1 or 2;

X is a bond or, when n is 2, X may also be a NR⁹ group;

wherein R⁹ is as defined above;

when X is a bond R⁸ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, biphenyl or a 9-14 membered bicyclic or tricyclic heteroaryl group;

when X is a NR⁹ group R⁸ may additionally be phenyl, naphthyl or a 5-7 membered heteroaromatic ring; and

the R⁸ group is optionally substituted with one or more substituents selected from halo, C₁-C₆ alkyl, -O(C₁-C₆)alkyl, aryl, -O-aryl, heteroaryl, -O-heteroaryl,

-CON(R⁹)₂, -SOR⁹, -SO₂R⁹, SO₂N(R⁹)₂, -N(R⁹)₂, -NR⁹COR⁹, -CO₂R⁹, -COR⁹, -SR⁹,

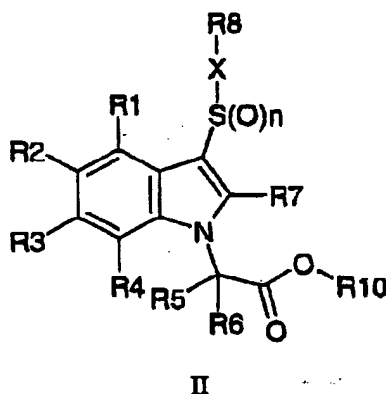
-OH, -NO₂ or -CN;

wherein R⁹ is as defined above;

or a pharmaceutically acceptable salt, hydrate, solvate, complex or prodrug thereof.

5

2. A compound of general formula (II):



10 wherein R¹, R², R³, R⁴, R⁵, R⁶, n, X, R⁷ and R⁸ are as defined for general formula (I);

R¹⁰ is C₁-C₆ alkyl, aryl, (CH₂)_mOC(=O)C₁-C₆alkyl, (CH₂)_mN(R¹¹)₂,
CH((CH₂)_mO(C=O)R¹²)₂;

m is 1 or 2;

R¹¹ is hydrogen or methyl;

15 R¹² is C₁-C₁₈ alkyl.

3. A compound as claimed in claim 1 or claim 2 wherein, independently or in any combination:

R¹ is halo or hydrogen;

20 R² is halo or hydrogen;

R³ is halo or hydrogen;

R⁴ is halo or hydrogen.

4. A compound as claimed in any one of claims 1 to 3 wherein R¹, R³ and R⁴ are
25 hydrogen and R² is halo.

5. A compound as claimed in claim 4 wherein R^2 is fluoro.
6. A compound as claimed in any one of claims 1 to 5 wherein R^5 and R^6 are
5 each independently hydrogen or C_1 - C_4 alkyl.
7. A compound as claimed in claim 6 wherein at least one of R^5 and R^6 are hydrogen.
- 10 8. A compound as claimed in claim 7 wherein both R^5 and R^6 are hydrogen.
9. A compound as claimed in any one of claims 1 to 8 wherein R^7 is H or C_1 - C_6 alkyl.
- 15 10. A compound as claimed in claim 9 wherein R^7 is methyl.
-
11. A compound as claimed in any one of claims 1 to 10 wherein n is 2.
12. A compound as claimed in any one of claims 1 to 11 wherein X is a bond and
20 R^8 is C_1 - C_6 alkyl, biphenyl or a bicyclic heteroaryl group, any of which may be substituted with halogen, phenyl, $-\text{CO}_2R^9$ $\text{CON}(R^9)_2$ or $-\text{SO}_2R^9$, where R^9 is as defined above.
13. A compound as claimed in claim 12 wherein R^8 is C_1 - C_4 alkyl, biphenyl, a
25 bicyclic heteroaryl group or a 5-7 membered heterocyclic ring, any of which may be substituted with phenyl, $-\text{CO}_2R^9$ $\text{CON}(R^9)_2$ or $-\text{SO}_2R^9$, where R^9 is H or C_1 - C_4 alkyl.
14. A compound as claimed in any one of claims 1 to 11 wherein X is NR^9 , R^9 is H or methyl and R^8 is:
30 phenyl optionally substituted with one or more halo, C_1 - C_6 alkyl or $-\text{O}(C_1$ - C_6 alkyl) groups;

C₁-C₆ alkyl, optionally substituted with aryl; or
heteroaryl.

15. A compound as claimed in claim 14, wherein R⁸ is phenyl, benzyl or pyridyl,
any of which may optionally be substituted with one or more halo, methyl or
methoxy groups.

16. [3-(Butane-1-sulfonyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
3-(Biphenyl-4-sulfonyl)-5-fluoro-2-methyl-indol-1-yl]-acetic acid
10 (3-Carboxymethanesulfonyl-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(3-Carbamoylmethanesulfonyl-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(5-Fluoro-3-(2-methanesulfonyl-ethanesulfonyl)-2-methyl-indol-1-yl)-acetic acid
(3-(Benzothiazole-2-sulfonyl)-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(3-(Benzothiazole-2-sulfinyl)-5-fluoro-2-methyl-indol-1-yl)-acetic acid
15 (5-Fluoro-2-methyl-3-(quinoline-2-sulfonyl)-indol-1-yl)-acetic acid
(5-Fluoro-2-methyl-3-(quinolin-8-ylsulfonyl)-indol-1-yl)-acetic acid
(5-Fluoro-2-methyl-3-phenylmethanesulfonyl-1H-indol-1-yl)-acetic acid
(3-(4-Chloro-phenylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(3-(3-Chloro-phenylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl)-acetic acid
20 (3-(4-Fluoro-phenylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(3-(2-Chloro-phenylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(3-Benzylsulfamoyl-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(5-Fluoro-3-(2-methoxy-phenylsulfamoyl)-2-methyl-indol-1-yl)-acetic acid
(5-Fluoro-3-(4-methoxy-phenylsulfamoyl)-2-methyl-indol-1-yl)-acetic acid
25 (5-Fluoro-2-methyl-3-phenylsulfamoyl-indol-1-yl)-acetic acid
(3-(3,4-Dichloro-benzylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(5-Fluoro-3-(3-methoxy-phenylsulfamoyl)-2-methyl-indol-1-yl)-acetic acid
(5-Fluoro-2-methyl-3-*m*-tolylsulfamoyl-indol-1-yl)-acetic acid
(5-Fluoro-2-methyl-3-*p*-tolylsulfamoyl-indol-1-yl)-acetic acid
30 (3-(4-Chloro-benzylsulfamoyl)-5-fluoro-2-methyl-indol-1-yl)-acetic acid
(3-(Benzyl-methyl-sulfamoyl)-5-fluoro-2-methyl-indol-1-yl)-acetic acid

[5-Fluoro-2-methyl-3-(pyridin-3-ylsulfamoyl)-indol-1-yl]-acetic acid;
or the C₁-C₆ alkyl, aryl, (CH₂)_mOC(=O)C₁-C₆alkyl, (CH₂)_mN(R¹¹)₂,
CH((CH₂)_mO(C=O)R¹²)₂ esters of any of the above; wherein

m is 1 or 2;

5 R¹¹ is hydrogen or methyl;

R¹² is C₁-C₁₈ alkyl.

17. A process for the preparation of a compound of general formula (I) as
claimed in any one of claims 1 to 13 or 16 wherein n is 1 or 2 and X is a bond, the
10 process comprising treating a compound of general formula (Ia), which is a
compound of general formula (I) wherein n is 0 and X is a bond, by oxidation with a
suitable oxidising agent.

18. A process for the preparation of a compound of general formula (I) as
15 claimed in any one of claims 1 to 16, the process comprising reacting a compound of
general formula (II) as defined in claim 2 and wherein R¹⁰ is C₁-C₆ alkyl with a base.

19. A compound as claimed in any one of claims 1 to 16 for use in medicine.

20. A compound as claimed in any one of claims 1 to 16 for use in the treatment
of allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic
dermatitis, contact hypersensitivity (including contact dermatitis), conjunctivitis,
especially allergic conjunctivitis, eosinophilic bronchitis, food allergies, eosinophilic
gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease,
25 mastocytosis, another PGD₂-mediated disease, for example autoimmune diseases
such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne,
multiple sclerosis, allograft rejection, reperfusion injury and chronic obstructive
pulmonary disease; or rheumatoid arthritis, psoriatic arthritis or osteoarthritis.

30 21. The use of a compound as claimed in any one of claims 1 to 16 in the
preparation of an agent for the treatment or prevention allergic asthma, perennial

allergic rhinitis, seasonal allergic rhinitis, atopic dermatitis, contact hypersensitivity (including contact dermatitis), conjunctivitis, especially allergic conjunctivitis, eosinophilic bronchitis, food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis, another PGD₂-mediated disease, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury and chronic obstructive pulmonary disease; or rheumatoid arthritis, psoriatic arthritis or osteoarthritis.

22. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 16 together with a pharmaceutical excipient or carrier.

23. A composition as claimed in claim 22 formulated oral, rectal, nasal, bronchial (inhaled), topical (including eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration.

24. A composition as claimed in claim 23 formulated for oral, nasal, bronchial or topical administration.

25. A composition as claimed in any one of claims 22 to 24 containing one or more additional active agents useful in the treatment of diseases and conditions mediated by PGD₂ at the CRTH2 receptor.

26. A composition as claimed in claim 25, wherein the additional active agents are selected from:

β₂ agonists such as salmeterol;

corticosteroids such as fluticasone;

antihistamines such as loratidine;

leukotriene antagonists such as montelukast;

anti-IgE antibody therapies such as omalizumab;

anti-infectives such as fusidic acid (particularly for the treatment of atopic

dermatitis);

anti-fungals such as clotrimazole (particularly for the treatment of atopic dermatitis);
immunosuppressants such as tacrolimus and particularly pimecrolimus in the case of
inflammatory skin disease;

- 5 other antagonists of PGD_2 acting at other receptors such as DP antagonists;
inhibitors of phosphodiesterase type 4 such as cilonilast;
drugs that modulate cytokine production such as inhibitors of $\text{TNF}\alpha$ converting
enzyme (TACE);
drugs that modulate the activity of Th2 cytokines IL-4 and IL-5 such as blocking
10 monoclonal antibodies and soluble receptors;
PPAR- γ agonists such as rosiglitazone;
5-lipoxygenase inhibitors such as zileuton.

27. A process for the preparation of a pharmaceutical composition as claimed in
15 any one of claims 22 to 26 comprising bringing a compound as claimed in any one of
claims 1 to 16 in conjunction or association with a pharmaceutically or veterinarily
acceptable carrier or vehicle.

28. A product comprising a compound as claimed in any one of claims 1 to 16
20 and one or more of the agents listed in claim 26 as a combined preparation for
simultaneous, separate or sequential use in the treatment of a disease or condition
mediated by the action of PGD_2 at the CRTH2 receptor.

29. The use as claimed in claim 21, wherein the agent also comprises an
25 additional active agent useful for the treatment of diseases and conditions mediated
by PGD_2 at the CRTH2 and/or DP receptor.

30. The use as claimed in claim 29, wherein the additional active agent is one of
the agents listed in claim 26.

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